PRVD2008-11

Proposed Re-evaluation Decision

Dodine

(publié aussi en français)

29 February 2008

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6605C
Ottawa, Ontario
K1A 0K9

Internet: pmra_publications@hc-sc.gc.ca
www.pmra-arla.gc.ca
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra_infoserv@hc-sc.gc.ca

Canada

ISBN: 978-0-662-48051-8 (978-0-662-48052-5)
Catalogue number: H113-27/2008-11E (H113-27/2008-11E-PDF)

© Her Majesty the Queen in Right of Canada, represented by the Minister of Health Canada, 2008

All rights reserved. No part of this information (publication or product) may be reproduced or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, or stored in a retrieval system, without prior written permission of the Minister of Public Works and Government Services Canada, Ottawa, Ontario K1A 0S5.

2008-04811/

Table of Contents

Overview 1
What Is the Proposed Re-evaluation Decision? 1
What Does Health Canada Consider When Making a Re-evaluation Decision? 1
What Is Dodine? 2
Health Considerations 3
Environmental Considerations 4
Measures to Minimize Risk 4
Next Steps 5

Science Evaluation 6

1.0 Introduction 6

2.0 The Technical Grade Active Ingredient, Its Properties and Uses 6
2.1 Identity of the Technical Grade Active Ingredient 6
2.2 Physical and Chemical Properties of the Technical Grade Dodine 7
2.3 Comparison of Use Patterns in Canada and the United States 7

3.0 Impact on Human Health and the Environment 8
3.1 Human Health 8
3.1.1 Occupational Exposure and Risk Assessment 9
3.1.2 Non-Occupational Exposure and Risk Assessment 10
3.1.3 Cumulative Effects 13
3.2 Environment 13
3.2.1 Environmental Risk Assessment 13
3.2.2 Toxic Substances Management Policy Considerations 16

4.0 OECD Status of Dodine 17

5.0 Proposed Re-evaluation Decision 17

6.0 Supporting Documentation 17

List of Abbreviations 19

Appendix I Registered Products Containing Dodine as of 1 October 2007 21

Appendix II Toxicological Endpoints for Dodine Health Risk Assessments 23

Appendix III Label Amendments for Products Containing Dodine 25

Appendix IV Inputs to Buffer Zone Models 29

Overview

What Is the Proposed Re-evaluation Decision?

After a re-evaluation of the fungicide dodine, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing continued registration for the sale and use of products containing dodine in Canada.

An evaluation of available scientific information found that products containing dodine do not present unacceptable risks to human health or the environment when used according to label directions. As a condition of the continued registration of dodine uses, new risk-reduction measures must be included on the labels of all products. No additional data are being requested at this time.

This proposal affects all end-use products containing dodine registered in Canada. Once the final re-evaluation decision is made, the registrants will be instructed on how to address any new requirements.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for dodine and presents the reasons for the proposed re-evaluation decision. It also proposes additional risk-reduction measures to further protect human health and the environment.

The information is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the assessment of dodine.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (please see contact information on the cover page of this document).

What Does Health Canada Consider When Making a Re-evaluation Decision?

The PMRA's pesticide re-evaluation program considers potential risks, as well as value, of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2001-03, *PMRA Re-evaluation Program*, presents the details of the re-evaluation activities and program structure.

---

[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

Dodine, one of the active ingredients in the current re-evaluation cycle, has been re-evaluated under Re-evaluation Program 1. This program relies as much as possible on foreign reviews, typically United States Environmental Protection Agency (USEPA) Reregistration Eligibility Decision (RED) documents. For products to be re-evaluated under Program 1, the foreign review must meet the following conditions:

- it covers the main science areas, such as human health and the environment, that are necessary for Canadian re-evaluation decisions;
- it addresses the active ingredient and the main formulation types registered in Canada; and
- it is relevant to registered Canadian uses.

Given the outcome of foreign reviews and a review of the chemistry of Canadian products, the PMRA will propose a re-evaluation decision and appropriate risk-reduction measures for Canadian uses of an active ingredient. In this decision, the PMRA takes into account the Canadian use pattern and issues (e.g. the federal Toxic Substances Management Policy (TSMP)).

Based on the health and environmental risk assessments published in the 2005 RED, the USEPA concluded that dodine was eligible for reregistration provided risk-reduction measures were adopted. The PMRA compared the American and Canadian use patterns and found the USEPA assessments described in this RED were an adequate basis for the proposed Canadian re-evaluation decision.

For more details on the information presented in this overview, please refer to the Science Evaluation section of this consultation document.

What Is Dodine?

Dodine, or dodecylguanidine acetate, is a salt of a strong base, dodecylguanidine. It is a fungicide that is used to control fungi infecting the leaves and fruit of certain crops. Farm workers may apply dodine using groundboom spray equipment and airblast equipment.

Dodecylguanidine hydrochloride is of similar chemical composition and properties as dodine and was considered bioequivalent and toxicologically the same as dodine in the 2005 RED. In Canada, dodecylguanidine hydrochloride is registered for similar industrial antimicrobial uses as in the U.S. (i.e. slimicide in recirculating cooling waters, pulp and paper mills, and preservative for paper products, coatings and adhesives) but is not currently under re-evaluation in Canada. Conclusions on risks are relevant for the purposes of the re-evaluation of dodine. This document does not represent a proposed re-evaluation decision for the registered Canadian uses of dodecylguanidine hydrochloride.

Health Considerations

Can Approved Uses of Dodine Affect Human Health?

Dodine is unlikely to affect your health when used according to revised label directions.

In Canada, people could be exposed to dodine by consuming food and water, working as a mixer/loader/applicator or by entering treated sites.

People could be exposed to dodecylguanadine hydrochloride indirectly from food packaged in paper or paper board made using this slimicide/preservative. Infants who wear disposable diapers impregnated with dodecylguanadine hydrochloride may also be exposed.

The PMRA considers two key factors when assessing health risks: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g. children and nursing mothers). Only uses for which exposure is well below levels that cause no effects in animal testing are considered acceptable for continued registration.

The USEPA concluded that dodine was unlikely to affect human health provided that risk-reduction measures were implemented. These conclusions apply to the Canadian situation, and equivalent risk-reduction measures are required.

Maximum Residue Limits

The *Food and Drugs Act* prohibits the sale of food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in or on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Dodine is currently registered in Canada for use on apples, cherries, pears and strawberries, and could be used in other countries on crops that are imported into Canada. Where no specific MRL has been established, a default MRL of 0.1 ppm applies, which means that pesticide residues in a food commodity must not exceed 0.1 ppm. However, changes to this general MRL may be implemented in the future, as indicated in Discussion Document DIS2006-01, *Revocation of 0.1 ppm as a General Maximum Residue Limit for Food Pesticide Residues [Regulation B.15.002(1)]*. If and when the general MRL is revoked, a transition strategy will be established to allow permanent MRLs to be set.

Environmental Considerations

What Happens When Dodine Is Introduced Into the Environment?

Dodine is unlikely to affect non-target organisms when used according to revised label directions.

Terrestrial and aquatic non-target organisms could be exposed to dodine in the environment. Environmental risk is assessed by the risk quotient method: the ratio of the estimated environmental concentration to the relevant effects endpoint of concern. The resulting risk quotients are compared to corresponding levels of concern. A risk quotient less than the level of concern is considered a negligible risk to non-target organisms, whereas a risk quotient greater than the level of concern indicates some degree of risk.

The USEPA concluded that the reregistration of dodine was acceptable provided risk-reduction measures to further protect the environment were implemented. These conclusions apply to the Canadian situation, and equivalent risk-reduction measures are required. Furthermore, the PMRA will require aquatic and terrestrial buffer zones for liquid and wettable powder formulations of dodine to protect aquatic organisms and terrestrial plants from spray drift.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law. As a result of the re-evaluation of dodine, the PMRA is proposing further risk-reduction measures for product labels.

Human Health

- Additional protective equipment to protect mixer/loader/applicators
- A restricted-entry interval to protect workers re-entering treated sites

Environment

- Additional advisory label statements to reduce potential surface and groundwater contamination
- Buffer zones to protect non-target, sensitive aquatic and terrestrial habitats
- Changes to the maximum single application rate and to limit the number of yearly applications

Next Steps

Before making a final re-evaluation decision on dodine, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Re-evaluation Decision[2] document that will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

"Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Science Evaluation

1.0 Introduction

Dodine belongs to the M7 group of guanidine fungicides and is used for the control of pathogenic fungi affecting the foliage and fruit of certain crops. Dodine is thought to exhibit multisite action and has both curative and protective modes of action.

Following the re-evaluation announcement for dodine, the registrant of the technical grade dodine in Canada indicated that it intended to provide continued support for all uses included on the labels of commercial end-use products in Canada.

The PMRA used recent assessments of dodine from the United States Environmental Protection Agency (USEPA). The USEPA Reregistration Eligibility Decision (RED) document for dodine, dated September 2005, as well as other information on the regulatory status of dodine in the United States can be found on the USEPA Pesticide Registration Status page at www.epa.gov/pesticides/reregistration/status.htm.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient

Common name	Dodine
Function	Fungicide
Chemical family	Guanidine
Chemical name	
1 **International Union of Pure and Applied Chemistry (IUPAC)**	1-Dodecylguanidinium acetate
2 **Chemical Abstracts Service (CAS)**	Dodecylguanidine monoacetate
CAS Registry Number	197142
Molecular formula	$C_{15}H_{33}N_3O_2$
Structural formula	
Molecular weight	287.4

Purity of the technical grade active ingredient	98% nominal (lower limit: 95%; upper limit:100%)
Registration Number	21919

Based on the manufacturing process, the product is not expected to contain impurities of human health or environmental concern as identified in Regulatory Directive DIR98-04, *Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient or an Integrated System Product*, Section 2.13.4 or Toxic Substances Management Policy (TSMP) Track 1 substances as identified in Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, Appendix II.

2.2 Physical and Chemical Properties of the Technical Grade Dodine

Property	Result
Vapour pressure	$\leq 1.3 \times 10^{-10}$ mPa
UV–visible spectrum	No absorption between 290–750 nm
Solubility in water	>100 ppm
n-Octanol–water partition coefficient	Log $K_{ow} < 3$
Dissociation constant	Not applicable

2.3 Comparison of Use Patterns in Canada and the United States

Dodine is a fungicide used for the control of pathogenic fungi affecting the foliage and fruit of apple, cherry, pear and strawberry crops. Application timing varies with each crop as follows:

- Apples from the silver tip through to the calyx stage at five- to seven-day intervals.
- Cherries from petal fall until seven days before harvest at seven- to 10-day intervals.
- Pears from pre-bloom through to first cover at five- to seven-day intervals.
- Strawberries typically one month after planting at seven-day intervals.

Dodine is applied with a maximum application rate of up to 2.1 kg a.i./ha on apples and pears and up to 1.46 kg a.i./ha on cherries and strawberries. The end-use products are formulated as wettable powders and a liquid, and are applied using groundboom sprayers and airblast spray equipment.

Dodecylguanidine hydrochloride, a salt of similar chemical composition and properties, was considered bioequivalent and toxicologically the same as dodine and was included with dodine in the 2005 RED for the purpose of reassessing tolerances. As a result of the tolerance reassessment, non-occupational sources of exposure to dodine were aggregated with those of dodecylguanadine hydrochloride.

The American and Canadian dodine and dodecylguanadine hydrochloride use patterns were compared. Dodine may be applied to the same fruit crops in Canada as in the United States. U.S. rates are higher than, or equivalent to, Canadian rates and are applied with similar frequency in the growing season. In Canada, dodecylguanidine hydrochloride is registered for similar industrial antimicrobial uses (i.e. slimicide in recirculating cooling waters and pulp and paper mills, preservative for paper products, coatings and adhesives). The application methods and rates that Canadians use for these pesticides are among those registered in the United States. Based on this comparison of use patterns, it was concluded that the USEPA RED for dodine is an adequate basis for the re-evaluation of uses of dodine in Canada.

All current uses are being supported by the registrant and were therefore considered in the re-evaluation of dodine. Appendix I lists all dodine products that are registered as of 1 October 2007 under the *Pest Control Products Act*.

3.0 Impact on Human Health and the Environment

The USEPA concluded that the end-use products formulated with dodine met the safety standards under the American *Food Quality Protection Act* and would not pose unreasonable risks or adverse effects to humans and the environment if used according to revised label directions.

3.1 Human Health

Toxicology studies in laboratory animals describe potential health effects resulting from various levels of exposure to a chemical and identify dose levels at which no effects are observed. Unless there is evidence to the contrary, it is assumed that effects observed in animals are relevant to humans and that humans are more sensitive to effects of a chemical than the most sensitive animal species.

Dodine and dodecylguanidine hydrochloride were expected to behave similarly in most environmental conditions and under physiological conditions based on their structural formulae. Thus data for dodine were considered representative of dodecylguanidine hydrochloride and vice versa. For the toxicological endpoints used by the USEPA in the assessment of risk to human health, see Appendix II.

Exposure to dodine may occur through consumption of food and water, while working as a mixer/loader/applicator or by entering treated sites. Exposures to dodecylguanidine hydrochloride to be aggregated with those of dodine may occur from consumption of food (packaged in paper made with this chemical) and water. Exposure can also result from homeowners using paint treated with dodecylguanidine hydrochloride. In addition to these routes of exposure, infants may also be exposed via diapers impregnated with dodecylguanidine hydrochloride. When assessing health risks, the PMRA considers two key factors: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g. children and nursing mothers).

3.1.1 Occupational Exposure and Risk Assessment

Occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies being used to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating safety factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

Workers can be exposed to dodine when mixing, loading or applying the pesticide and when entering a treated site to conduct activities such as scouting or handling treated crops.

3.1.1.1 Mixer/Loader/Applicator Exposure and Risk

It was determined that there were several exposure scenarios for occupational handlers of dodine. Specifically, exposure via the dermal and inhalation routes could occur during mixing and loading for application by groundboom and airblast equipment.

Among the scenarios assessed in the RED, the following exposure scenarios were considered relevant to the Canadian situation:

- mixing/loading liquids or wettable powders for groundboom or airblast applications
- applications of liquids and wettable powders by groundboom and airblast

Handler exposure analyses were performed using surrogate data from the Pesticide Handlers Exposure Database (PHED V1.1), assuming baseline attire (long pants, long-sleeved shirt, shoes and socks) during all activities, and chemical-resistant gloves during mixing/loading.

The relevant occupational handler scenarios that the U.S. assessed resulted in MOEs greater than 100 and thus are not of concern.

The RED adequately addressed exposure scenarios associated with the uses of products containing dodine in Canada, and conclusions derived from the RED apply to the Canadian situation. Based on this, the PMRA requires that handlers must wear a long-sleeved shirt and long pants during all activities as well chemical-resistant gloves and a chemical-resistant apron during mixing/loading and clean-up and repair activities. Additional instructions concerning good hygiene practices are also required on labels. The proposed label amendments are listed in Appendix III.

3.1.1.2 Postapplication Exposure and Risk

The postapplication occupational risk assessment considered exposures to workers entering treated sites. Short-term (one to six months) postapplication exposure to workers re-entering areas treated with dodine to perform specific activities could potentially occur. For all registered scenarios of dodine use, chemical-specific dislodgeable foliar residue (DFR) and activity-specific transfer coefficients (TC) were used to analyze postapplication exposure from contact with treated foliage at various times after treatment. DFR data include the amount of

residue that can be dislodged or transferred from a surface, such as the leaves of a plant. A TC is a factor that relates worker exposure to dislodgeable residues. TCs are specific to a given crop and activity combination (e.g. hand harvesting apples, scouting late season cotton) and reflect standard work clothing worn by adult agricultural workers. Postapplication exposure activities include harvesting, thinning, pruning, scouting and irrigating trees.

The results indicated that the postapplication occupational exposure and risks are not of concern. MOEs ranged from 99 (for hand activities such as harvesting, propping, pruning and thinning in California peach orchards) to 57 509 (for propping ornamental trees) approximately 24 hours after application to all crops. However, based on the EPA's classification of dodine as a Category I eye irritant, a restricted-entry interval of 48 hours was required to adequately mitigate the potential eye and dermal exposure to all postapplication workers.

The RED adequately addressed postapplication exposure scenarios associated with the Canadian uses of dodine. Conclusions derived from the RED are considered to be applicable to the Canadian situation. Based on this, the PMRA requires a restricted-entry interval of 48 hours to further protect workers from postapplication exposure. Proposed label amendments are listed in Appendix III.

3.1.2 Non-Occupational Exposure and Risk Assessment

3.1.2.1 Residential Exposure

Residential exposure is estimated using the MOE approach described in Section 3.1.1. The toxicological endpoints selected by the USEPA for assessment of risk from residential exposure are summarized in Appendix II.

Residential uses of dodine are not registered in the U.S. and thus no residential exposure was expected.

However, there could be potential residential exposure to dodecylguanidine hydrochloride from preserved paint products and impregnated disposable diapers. Exposures and risks to residential painters were assessed using the dermal and inhalation exposure in the PHED V1.1. Short-term exposure duration was considered since residential painters typically paint on an intermittent basis. All of the combined dermal and inhalation MOEs for residential painters were greater than 100 and did not exceed the EPA's level of concern for residential uses of dodecylguanidine hydrochloride.

Potential postapplication exposure (inhalation and dermal) from paint was expected to be negligible and was not assessed quantitatively. The paint is expected to dry within a day. Therefore, dermal contact with wet paint is unlikely and dodecylguanidine hydrochloride is not likely to generate sufficient vapour to cause an inhalation concern (based on low vapour pressure less than 1×10^{-7} mm Hg at 25°C) to individuals occupying recently treated areas.

Exposure to dodecylguanidine hydrochloride may also be from its bacteriostatic uses in the manufacture of the absorbent material used in diapers. MOEs for infants who wear diapers impregnated with dodecylguanidine hydrochloride were assessed and did not exceed the USEPA's level of concern.

The RED adequately addressed exposure scenarios associated with the residential uses of dodecylguanidine hydrochloride (i.e. in paint and on fibre used in the manufacture of disposable diapers) in Canada; thus, the conclusions derived from the RED are considered applicable to the Canadian situation. The PMRA requires no further mitigation measures with respect to residential exposure.

3.1.2.2 Exposure From Food and Drinking Water

No acute dietary toxicity endpoint was identified and there was no evidence of carcinogenicity in the dodine database; thus, no acute dietary assessments or cancer assessments have been conducted by the USEPA.

The USEPA identified toxicity endpoints (Appendix II) for use in the chronic dietary risk assessment. The endpoints were also appropriate to determine risks from potential exposure to dodine in drinking water.

Chronic dietary risk is estimated by determining how much of a pesticide residue may be ingested with the daily diet and comparing this potential exposure to an acceptable daily intake, which is the dose at which an individual could be exposed over the course of a lifetime and expect no adverse health effects. The acceptable daily intake is referred to as the ADI in Canada, and, in the RED, it is expressed as the chronic population adjusted dose (cPAD). The ADI is based on a relevant endpoint from toxicology studies and on safety factors protective of the most sensitive subpopulation.

Chronic dietary risks (food and water) from dodine were estimated using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03), which uses food consumption data from USDA's Continuing Survey of Food Intakes by Individuals (CSFII) from 1994–1996 and 1998. The food assessment was based on tolerance values for registered commodities, DEEM default processing factors and a cPAD of 0.02 mg/kg bw/day, based on a NOAEL of 2 mg/kg bw/day from a dog study. Potential drinking water exposure was modelled based on five aerial applications of dodine at 2.91 kg a.i./ha.

Tier 1 estimated drinking water concentrations (EDWCs) for surface water were generated using the Fifra Index Reservoir Screening Tool (FIRST), while groundwater concentrations were estimated using the Tier I Screening Concentration In Ground Water (SCI-GROW) 2.3 model.

Dietary risks (food and water) from dodine were not of concern for the general population or any subpopulation. Risk estimates were 3% of the cPAD for the general population and 16% of the cPAD for non-nursing infants and children one to two years old, the highest exposed subgroup.

These estimates are considered very conservative because they were conducted using tolerance level values, assumed treatment of all pome and stone fruits (not just those appearing on the currently registered U.S. labels), and were based on drinking water exposure in the worst-case scenario of five aerial applications.

Concentrations of dodecylguanidine hydrochloride were estimated for receiving surface waters from the modelled once-through use in cooling water towers. The USEPA concluded that the risk from chronic exposure to dodecylguanidine hydrochloride in drinking water would be negligible and did not consider contributions from dodecylguanidine hydrochloride in the drinking water assessment.

The dietary risks from dodecylguanidine hydrochloride used as an indirect food additive in paper products were also calculated, using endpoints from the dodine food exposure assessment.

These paper uses did not exceed any level of concern for chronic exposure durations. The combined dietary intake of dodecylguanidine hydrochloride represented 13% of the cPAD for adults and 45.5% of the cPAD for children.

The calculated dietary exposures from dodecylguanidine hydrochloride use as an indirect food additive for adults and children were aggregated with the dodine dietary exposures (food and water) and did not exceed the USEPA's level of concern.

3.1.2.3 Aggregate Risk Assessment

Aggregate risk combines the different routes of exposure to dodine (i.e. from food, water and residential exposures). These include non-occupational exposures to dodecylguanidine hydrochloride. Acute and chronic aggregate risk assessments are comprised of contributions from food and drinking water exposures. Short-term and intermediate aggregate risk assessments are comprised of contributions from food, drinking water and non-occupational exposure (dermal, inhalation).

Aggregate risks (short-, intermediate- or chronic-term) from non-occupational exposures to dodine and dodecylguanidine hydrochloride for all population groups did not exceed any level of concern.

Short-term aggregate risks were conservatively estimated (MOE approach) for adults, taking into account dodine dietary exposures (food and water) as well as potential dodecylguanidine hydrochloride exposure from treated paper that comes in contact with food (indirect food additive) and from applying paint containing dodecylguanidine hydrochloride as a preservative. The short-term aggregate MOE for adults is 574 and did not exceed the USEPA's level of concern. Short-, intermediate- and long-term aggregate risks were estimated for infants, taking into account dodine dietary exposures (food and water) as well as potential dodecylguanidine hydrochloride exposure from paper use and wearing diapers impregnated with dodecylguanidine hydrochloride. The total aggregate MOE for infants for all durations is 132 and does not exceed the USEPA's levels of concern (LOCs).

Overall, the Canadian aggregate exposure scenarios were adequately addressed by the USEPA aggregate risk assessment. Therefore, the USEPA aggregate exposure conclusions are considered applicable to the uses of dodine in Canada.

3.1.3 Cumulative Effects

The USEPA has not determined whether dodine has a common mechanism of toxicity with other substances or whether it shares a toxic metabolite produced by other substances. Therefore, it was assumed that dodine does not share a common mechanism of toxicity with other substances, and a cumulative risk assessment was not required.

3.2 Environment

3.2.1 Environmental Risk Assessment

The environmental fate and transport characterization of dodine and dodecylguanidine hydrochloride was addressed as a combined data set because these compounds are expected to behave the same under environmental conditions (in water and moist soil). Both compounds are water-soluble salts of a strong base (dodecylguanadine), which should dissociate to the same degree under any normal environmental conditions. As strong bases, these compounds will be completely dissociated in aqueous solutions at normal environmental pHs. At the low concentrations present in the environment and in the presence of moisture, both compounds would be present as the dodecylguanidium cation and either acetate or chloride ion.

Dodine was found to be immobile in sandy soils and was generally not expected to persist in aerobic soils. The potential to reach aquatic ecosystems in runoff is limited. However, it may be transported off site to aquatic ecosystems, bound to eroded sediment or via spray drift during aerial, airblast or ground spray applications. Once in aerobic aquatic environments, dodine is likely to persist.

The USEPA considered toxicity data from both dodine and dodecylguanidine hydrochloride studies, selecting the more sensitive endpoints of the two chemicals.

To assess the ecological risk of dodine to both terrestrial and aquatic non-target plants and animals, the USEPA calculated risk quotients (RQs) based on appropriate toxicity endpoints and expected environmental concentrations (EECs) and compared the resulting RQs to corresponding LOCs.

Risk assessments for insects were not performed because dodine was found to be practically non-toxic to honey bees on an acute basis. As a result, the potential for dodine to have adverse effects on pollinators and other beneficial insects was expected to be low, and significant acute and chronic risks to insects were also not expected.

Tier II aquatic EECs were estimated using the surface water model from Pesticide Root Zone Model and the Exposure Analysis Modelling System (PRZM/EXAMS). All dodine uses were considered in this assessment (apples, cherries, peaches, pears, pecans, strawberries, walnuts,

crab apples and ornamentals). Modelling was done using the maximum labelled rate (1.3 kg a.i./ha for strawberries to 2.91 kg a.i./ha for peaches, pecans and walnuts), maximum number of applications per year (five to six) and minimum application interval (five to 10 days) for the various scenarios, also accounting for different geographical locations and agricultural practices. All scenarios were simulated with aerial applications, with the strawberry scenario being the only groundboom spray application modelled.

The screening level assessment indicated that acute and chronic RQs were generally not of concern for fish (freshwater or marine), although there was a slight exceedance of the level of concern (LOC) from six aerial applications to apples at a rate of 2.2 kg a.i./ha. Based on limited data, the risks to estuarine/marine fish was thought to be unlikely, due to the low chronic risks to freshwater fish (RQs ranged from 0.0–0.08). The acute RQs for freshwater invertebrates exceeded LOCs for all modelled uses except application to strawberries (RQs ranged from 0.34–2.4). Based on a study of sediment-dwelling larvae of *Chironomus riparius*, RQs did not exceed any LOC. Thus chronic risk to freshwater benthic invertebrates was expected to be low. The acute risk LOCs for listed estuarine/marine invertebrates was exceeded for all scenarios. RQs ranged from 0.1 to 0.72, except for strawberries (RQ = 0, with application rate of 1.46 kg a.i./ha).

The USEPA considered vascular and nonvascular aquatic plants together, given the high toxicity of dodine to nonvascular plants and lack of sufficient toxicity data for aquatic vascular plants. There were potential acute and chronic risks to aquatic plants based on LOC exceedances. Acute RQs (10 for strawberries to 524 for apples) exceeded LOCs for nonvascular aquatic plants for most uses (except strawberries), and all scenarios exceeded the chronic LOCs.

The greatest contribution to predicted dodine exposure in water is from erosion, particularly at sites that are vulnerable to sediment loss. As such, to reduce the potential effects to aquatic plants, the EPA required a label statement to limit the use of dodine on areas where erosion is high.

Exposure to terrestrial receptors was estimated using the screening-level exposure model TREX (v.1.1), considering spray applications of dodine using maximum application rates, the maximum number of applications and minimum application intervals for all proposed uses. The assessment was dose-based and calculated the approximate exposure associated with animals consuming certain dietary items. The estimates were based on a database of pesticide residue present on various food items as determined by the Kenaga nomogram and modified by Fletcher (Hoerger and Kenaga, 1972; Fletcher et al., 1994) and accounted for pesticide degradation.

Dodine exposure to terrestrial plants inhabiting both dry and semi-aquatic (wetland) habitats was estimated using EPA's Terr Plant (v1.0) model. The EECs were generated from one application at the maximum rate for a particular use and compound-specific solubility information. RQs were not calculated because of the lack of Tier II plant data.

All acute risk LOCs were exceeded for birds consuming short grass, broadleaf plants and small insects across most weight classes for all modelled scenarios and application rates (with RQs ranging from 0.06 to 5.6). In addition, acute RQ values exceeded LOCs for acute risk to birds

that consume fruits, pods, seeds or large insects at application rates for all modelled scenarios, except crab apples, for the smallest weight class, and in some cases for the medium weight class (with RQ exceedances ranging from 0.12–0.35). Chronic LOCs were exceeded for birds that consume short grass, tall grass, broadleaf plants and small insects for all modelled scenarios and application rates (2.29–14.56 kg a.i./hectare/yr). Risk to birds from chronic exposure was likely with RQs ranging from <LOC to 4.3.

All acute LOCs (RQs ranging from <LOC to 0.35) were exceeded for mammals consuming short grass, tall grass, broadleaf plants and small insects across most weight classes for all modelled scenarios and application rates (2.29–14.56 kg a.i./hectare/yr). The chronic LOCs were exceeded (ranging from 1.0–34) for wild mammals that consume short grass, tall grass, broadleaf plants and small insects across all assessed weight classes for all modelled scenarios and application rates. For birds consuming fruits, pods or large insects, chronic LOCs were exceeded for most uses of dodine, particularly for smaller birds. No RQs exceeded any chronic LOCs for seed-eating mammals.

Although the USEPA's screening level ecological and environmental risk assessment for registered uses of dodine indicated potential exceedances of the LOC for birds, mammals and aquatic invertebrates, overall, the ecological risk associated with dodine's use is expected to be limited based on the use pattern and usage information. Many of the potential exceedances are based on calculations that assume worst-case conditions. Typical U.S. usage data indicated that aerial application is uncommon for dodine; it is used only when orchard floors are impassable for ground equipment. Orchard fungicides are most frequently applied with an airblast system to ensure complete coverage of the plant surface.

The U.S. registrant agreed to a reduction in the maximum single application rate for peaches, pecans and walnuts, and in the maximum seasonal rates for all other crops, except strawberries.

The potential exposure and risk to the environment from the registered Canadian uses of dodine was adequately addressed in the RED risk assessments. There are no registered aerial uses of dodine in Canada. The risk profile generated by the USEPA modelled the use of maximum rates of aerial application to orchards. This is considered relevant to the Canadian situation because it represents a conservative estimation of exposure to the environment from airblast application in Canadian orchards. Information gathered from Canadian users indicates that dodine is typically applied less frequently during the growing season than in the U.S. Conclusions and resulting mitigation measures derived from the USEPA RED are considered relevant to the Canadian situation. Canadian application rates are already at or below the reduced rates in the U.S.

Based on concerns for aquatic and terrestrial non-target species, the USEPA limited the frequency and maximum application rate of dodine to reduce ecological exposure.

The American use pattern for dodine encompasses the Canadian use pattern, and the USEPA's risk-reduction measures should be applied to Canadian products containing dodine. The USEPA's mitigation measures must be adapted to the Canadian situation as follows:

- Canadian product labels must specify the maximum number of applications in a year for a given rate and include a statement to reduce runoff in areas prone to erosion.

- The PMRA will require terrestrial and aquatic buffer zones for the liquid and wettable powder formulations of dodine to protect aquatic organisms and terrestrial plants from spray drift.

Proposed label amendments are listed in Appendix III. Inputs to buffer zone models are described in Appendix IV.

3.2.2 Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the 1995 federal Toxic Substances Management Policy, which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. The policy provides decision makers with direction and sets out a science-based management framework to ensure that federal programs are consistent with its objectives. One of the key management objectives is virtual elimination from the environment of toxic substances that result predominantly from human activity and that are persistent and bioaccumulative. These substances are referred to in the policy as Track 1 substances.

The federal Toxic Substances Management Policy and PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, were taken into account during the re-evaluation of dodine. The PMRA has reached the following conclusions:

- Dodine is not bioaccumulative. The *n*-octanol–water partition coefficient (log K_{ow}) is 1 at pH 7.7, which is below the TSMP Track 1 cut-off criterion of ≥ 5.0.

- Dodine was not found to be persistent. The aerobic soil half-life is 22.3 days, which is below the TSMP Track 1 criterion of 180 days. Dodine does not meet all Track 1 criteria; thus, it is not a candidate for Track 1 classification.

- Based on a review of the available chemistry information (see Section 2.1), the technical product is not expected to contain impurities of toxicological concern as identified in Regulatory Directive DIR98-04 or TSMP Track 1 substances as identified in Regulatory Directive DIR99-03, Appendix II.

No other impurities of toxicological concern as identified in Regulatory Directive DIR98-04, Section 2.13.4, or TSMP Track1 substances as identified in Regulatory Directive DIR99-03, Appendix II, are expected to be present in the technical product of dodine.

Formulant issues are being addressed through PMRA formulant initiatives and Regulatory Directive DIR2006-02, *Formulants Policy and Implementation Guidance Document*, published on 31 May 2006.

4.0 OECD Status of Dodine

Canada is part of the Organisation for Economic Co-operation and Development (OECD), which groups 30 member countries and provides governments with a setting in which to discuss, develop and perfect economic and social policies. They compare experiences, share information and analyses, seek answers to common problems, and work to co-ordinate domestic and international policies to allow for consistency in practices across nations.

Based on the current status of dodine in other OECD member countries, dodine has not been prohibited for use in any of the OECD member states.

5.0 Proposed Re-evaluation Decision

The PMRA has determined that dodine is acceptable for continued registration with the implementation of the proposed risk-reduction measures. These measures are required to further protect human health and the environment. Labels for the Canadian end-use products must be amended to include the label statements listed in Appendix III. A submission to implement label revisions will be required within 90 days of finalization of the re-evaluation decision. No additional data are being requested at this time.

6.0 Supporting Documentation

PMRA documents, such as Regulatory Directive DIR2001-03, and DACO tables can be found on our website at www.pmra-arla.gc.ca. PMRA documents are also available through the Pest Management Information Service. Phone: 1-800-267-6315 within Canada or 1-613-736-3799 outside Canada (long distance charges apply); fax: 613-736-3798; e-mail: pmra_infoserv@hc-sc.gc.ca.

The federal TSMP is available through Environment Canada's website at www.ec.gc.ca/toxics.

The USEPA RED document for dodine is available on the USEPA Pesticide Registration Status page at www.epa.gov/pesticides/reregistration/status.htm.

List of Abbreviations

µg	microgram(s)
ADI	acceptable daily intake
a.i.	active ingredient
atm	atmosphere(s)
bw	body weight
CAS	Chemical Abstracts Service
cm	centimetre(s)
CSFII	Continuing Survey of Food Intakes by Individuals
d	day(s)
DACO	data code
DEEM™	Dietary Exposure Evaluation Model
DFR	dislodgeable foliar residue
DT_{50}	dissipation time to 50%
EC_{25}	environmental concentration to 25%
EC_{50}	environmental concentration to 50%
EXAMS	Exposure Analysis Modeling System
F_0	parental generation (also abbreviated as P)
F_1	first filial generation
F_2	second filial generation
FQPA	*Food Quality Protection Act*
g	gram(s)
h	hour(s)
ha	hectare(s)
kg	kilogram(s)
K_{oc}	organic carbon partition coefficient
K_{ow}	*n*-octanol–water partition coefficient
L	litre(s)
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose to 50%
m	metre(s)
m^3	metre(s) cubed
min	minute(s)
mg	milligram(s)
mm	millimetre(s)
mm Hg	millimetre mercury
MOE	margin of exposure
MRL	maximum residue limit
NOAEL	no observed adverse effect level
nm	nanometre(s)
pH	-log10 hydrogen ion concentration
PHED	Pesticide Handlers Exposure Database
pKa	-log10 acid dissociation constant
PMRA	Pest Management Regulatory Agency
ppb	parts per billion
ppm	parts per million

PRVD	Proposed Re-evaluation Decision
PRZM	Pesticide Root Zone Model
Q_1^*	cancer potency factor
RED	Reregistration Eligibility Decision
REI	restricted-entry interval
RQ	risk quotient
TC	transfer coefficient
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
URMULE	User Requested Minor Use Label Expansion
USEPA	United States Environmental Protection Agency

Appendix I Registered Products Containing Dodine as of 1 October 2007

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee (%)
21919	Technical	Agriphar S.A.	Dodine Technical fungicide	Solid/dust	98
23296	Commercial	Agriphar S.A.	Syllit 65WP fungicide	Wettable powder	65
28351	Commercial	Agriphar S.A.	Syllit 400FL fungicide	Solution	402 g/L
15608	Commercial	Norac Concepts	Equal 65WP fungicide	Wettable powder	65

Page 22

Appendix II Toxicological Endpoints for Dodine Health Risk Assessments

Exposure Scenario (route and period of exposure)	Dose (mg/kg bw/day)	Study	Target UF/SF or MOE or Q_1^* [a]
Chronic dietary (non-cancer), all populations	Oral NOAEL of 2 mg/kg bw/day	Oral (dog)	UF = 100 FQPA SF = 1
	cRfD= 0.02 mg/kg bw/day		
Short- and intermediate-term occupational	NOAEL of 200 mg/kg bw/day	28-day dermal toxicity (rat)	MOE = 100
Short- and intermediate-term occupational	NOAEL of 10 mg/kg bw/day	Developmental Maternal (rat) Inhalation (100% absorption)	MOE = 100

[a] UF/SF refers to total of uncertainty and/or safety factors for dietary assessments. MOE refers to desired margin of exposure for occupational or residential assessments. Q_1^* refers to cancer potency factor.

Appendix III Label Amendments for Products Containing Dodine

The labels of end-use products in Canada must be amended to include the following statements to further protect workers and the environment:

I) The following statements must be included in the **PRECAUTIONS** section:

- All handlers must wear a long-sleeved shirt and long pants. In addition, wear chemical-resistant gloves and a chemical-resistant apron during mixing/loading activities. Chemical-resistant gloves should also be worn during repair and clean-up activities.
- Do not enter or allow worker entry into treated areas during the restricted-entry interval (REI) of 48 hours.
- Do not apply this product in a way that it will contact workers or other persons, either directly or through drift. Only handlers wearing personal protective equipment may be in the area being treated during application.
- Discard clothing or other absorbent materials that have been drenched or heavily contaminated with this product's concentrate. Do not reuse them.
- Users should remove clothing immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing.

II) The following statements must be included in the **DIRECTIONS FOR USE** section:

- **Apples**
  Do not apply more than 10.2 kg a.i./ha/year.
  Do not apply more than 2 applications per year at a rate of 2.2 kg a.i./ha/application.
  Do not apply more than 4 applications per year at a rate of 1.46 kg a.i./ha/application.
  Do not apply less than 7 days from the last application.
  Do not apply within 7 days of harvest.

  Cherries (sour and sweet)
  Do not apply more than 5.8 kg a.i./ha/year.
  Do not apply more than 2 applications per year at a rate of 1.46 kg a.i./ha/application.
  Do not apply more than 4 applications per year at a rate of 0.73 kg a.i./ha/application.
  Do not apply less than 7 days from the last application.
  Do not apply within 7 days of harvest.

Pears
Do not apply more than 10.2 kg a.i./ha/year.
Do not apply more than 2 applications per year at a rate of 2.2 kg a.i./ha/application.
Do not apply more than 4 applications per year at a rate of 1.46 kg a.i./ha/application.
Do not apply less than 7 days from the last application.
Do not apply within 7 days of harvest.

Strawberries
Do not apply more than 1.46 kg a.i./ha/application.
Do not apply more than 5 times per year.
Do not apply less than 7 days from the last application.
Do not apply within 14 days of harvest.

To reduce runoff from treated areas into aquatic habitats, consider the characteristics and conditions of the site before treatment. Site characteristics and conditions that may lead to runoff include but are not limited to the following: heavy rainfall, moderate to steep slope, bare soil, poorly draining soil (e.g. soils that are compacted or fine-textured, such as clay).

Avoid application of this product when heavy rain is forecast.

Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) classification of "fine". Boom height must be 60 cm or less above the crop or ground.

Airblast application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer rows. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side.

DO NOT apply by air.

Buffer zones:

Use of the following spray methods or equipment **DO NOT** require a buffer zone: hand-held or backpack sprayer, or spot treatment.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands), sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:				
			Freshwater Habitat of Depths:		Estuarine/Marine Habitats of Depths:		Terrestrial habitat
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than m	
Field sprayer*	Strawberries		70	35	2	1	1
Airblast	Apple, pear	Early growth stage	65	55	25	15	2
		Late growth stage	55	45	15	10	1
	Cherry	Early growth stage	60	50	20	10	2
		Late growth stage	50	40	10	5	1

* For field sprayer application, buffer zones can be reduced with the use of drift-reducing spray shields. When using a spray boom fitted with a full shield (shroud, curtain) that extends to the crop canopy, the labelled buffer zone can be reduced by 70%. When using a spray boom where individual nozzles are fitted with cone-shaped shields that are no more than 30 cm above the crop canopy, the labelled buffer zone can be reduced by 30%.

III) The following statements must be included in the **ENVIRONMENTAL HAZARDS** section.

TOXIC to aquatic organisms and non-target terrestrial plants. Observe buffer zones specified under DIRECTIONS FOR USE.

To reduce runoff from treated areas into aquatic habitats, avoid application to areas with a moderate to steep slope, compacted soil, or clay.

Avoid application when heavy rain is forecast.

Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

When a tank mixture is used, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture.

The label amendments presented above do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Additional information on labels of currently registered products should not be removed unless it contradicts the above label statements.

A submission to request label revisions will be required within 90 days of finalization of the re-evaluation decision.

Appendix IV Inputs to Buffer Zone Models

Ground Use Data (from Canadian labels)				
Crop	**Formulation Type**	**Method of Application**	**Number of Application**	**Maximum Application Rate (g a.i./ha)**
Apple, pear	Dry flowable	Airblast	6	2200
Cherries	Dry flowable	Airblast	6	1460
Strawberry	Dry flowable	Field sprayer	5	1460

Model Input Data for Aquatic Buffer Zones (from 2005 RED)		
Half-life for aquatic buffer zones	N/A	Assumed stable
Most sensitive freshwater species	Green algae *Selenastrum capricornutum*	½ EC_{50} = 0.475 µg a.i./L
Most sensitive estuarine/marine species	Mysid shrimp *Mysidopsis bahia*	½ LC_{50} = 29.7 µg a.i./L

Model Input Data for Terrestrial Buffer Zones (from 2005 RED)		
Half-life for terrestrial buffer zones	Soil degradation half-life	22.3 days
Most sensitive terrestrial plant species EC_{25} for vegetative vigour	Cabbage-seedling emergence	2914 g a.i./ha